

REMARKS/ARGUMENTS

Applicants request entry of the above amendments to Claims 1, 10, 11, 26, 27, 85 and 86 and entry of new Claims 90-93. With entry of the requested amendments and new claims, Claims 1, 10, 11, 23-27 and 85-93 are pending in the application.

Claims 1, 10, 11, 26, 27, 85 and 86 have been amended to recite smooth muscle, instead of vascular smooth muscle, in accordance with the claims and specification as originally filed (see, e.g., page 6, lines 11-20, and original Claims 1-3). Claim 26 has been amended to more clearly indicate the subject matter of the claim. The amendments to Claim 26 find support, for example, in the specification at page 8, lines 25-30 through page 9, lines 1-8; page 21, line 9 to page 22, line 2; original Claims 26 and 38; and elsewhere in the specification and claims as filed. Claim 27 has been amended to more clearly indicate the subject matter of the claim. The amendments to Claim 27 find support, for example, in the specification at page 8, lines 5-9, page 18, lines 18-22, page 42, lines 6-17, original Claims 27 and 39, and elsewhere in the specification and claims as filed.

New Claims 90-93 find support in the specification and claims as originally filed. Support for new Claims 90-93 may be found in the specification, for example, at page 9, lines 9-14, in original Claims 25-29, and elsewhere in the specification and claims as originally filed. In particular, new Claims 90-93 claim methods for inhibiting proliferation or migration of smooth muscle cells using the novel antibodies of the invention. Such methods are useful, for example, for inhibiting proliferation or migration of smooth muscle cells *in vitro* (e.g., Examples 2 and 3, pages 67-69), for use in methods for treating stenosis and related disorders *in vivo* (page 6, line 24 to page 7, line 2), and for use in methods for treating cancers *in vivo* (page 9, lines 1-2).

Applicants note that the methods of new Claims 90-93 recite antibodies produced by a hybridoma selected from the group of novel hybridoma cell lines HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number

PTA-2825). These antibodies, hybridoma cells and methods are not anticipated nor made obvious by any cited reference or combination of references.

No new matter is added by way of the amendments to the claims or by the new claims.

Claims 1, 10-11, 23-27 and 85-89 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for methods of inhibiting proliferation or migration of smooth muscle cells *in vitro* comprising administering an effective amount of antibody to native ErbB4 receptor.

Claims 1, 10-11, 23-27 and 85-80 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent Claims 1, 26, and 27 are alleged to be indefinite and ambiguous in the recitation of "treating said vascular smooth muscle with ... antibody antagonist ..." The Examiner alleges that it is unclear whether an antibody or whether an antagonist of said antibody is to be used.

Claim 26 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the Examiner alleging that the claim is indefinite and ambiguous in the recitation of the phrase "antibody binds essentially the same epitope as an antibody produced by ...," the phrase "essentially the same epitope" allegedly being unclear.

Claims 1, 10, 11, and 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681, for the reasons set forth in the previous Office Action mailed March 9, 2004.

Applicants respectfully traverse the rejections.

The Rejections of Claims 1, 10-11, 23-27 and 85-89 Under U.S.C. §112, First Paragraph

Claims 1, 10-11, 23-27 and 85-89 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for methods of inhibiting

proliferation or migration of smooth muscle cells *in vivo* comprising administering an effective amount of antibody to native ErbB4 receptor.

Applicants traversed the rejections to the *in vivo* claims in the amendment mailed on January 13, 2004, although the *in vivo* claims were canceled, and noted that Claim 1 was amended to refer to *in vitro* applications "solely to expedite prosecution of the pending application to issue.... "(page 5 of the amendment mailed on January 13, 2004). In addition, the limitation "vascular" was inserted in the claims in a previous amendment in an attempt to expedite prosecution of the application. The specification and claims as originally filed providing adequate support for *in vivo* claims, and prosecution of the pending application not having been expedited by the previous amendments, applicants reiterate their claim for methods for inhibiting proliferation or migration of smooth muscle cells, both *in vitro* and *in vivo*.

The Legal Standard

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555 at 1563, 19 USPQ2d 1111 at 1116 (Fed. Cir. 1991) and Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 45 USPQ 2d 1498 [Fed. Cir. 1998], and MPEP 2163.02). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See, e.g. Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

Applicants assert that they have met this requirement. Applicants emphasize that sufficient written description must be ascertained in view of one skilled in the art. "It is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in

the art will recognize that the applicant made the invention having those limitations" (*Martin v. Mayer*, 823 F.2d 500, 3 USPQ 2d 1333 [Fed. Cir. 1987])

It is well established that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims, see, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). It is also well established that if the art is such that a particular model is recognized as correlating to a specific condition, then reasonable correlation will be accepted, unless the Examiner provides evidence that such correlation does not exist. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). A rigorous or an invariable exact correlation is not a requirement. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir. 1985).

Applicants note that the Examiner has acknowledged that Claims 1, 10-11, 23-27 and 85-89 are "enabling for *in vitro* method of partially inhibiting proliferation or migration of vascular smooth muscle cells in cell culture, comprising administering an effective amount of antibody to native ErbB4 receptor" (Office action mailed September 9, 2004, page 3, paragraph number 6, lines 2-4). As discussed in previous responses, which are hereby incorporated by reference, Applicants pointed to language in the specification (page 6, lines 11-14, for example) in which it is stated that inhibition of excessive proliferation or migration of smooth muscle cells includes total inhibition, indicating Applicants' contemplation of at least partial as well as total inhibition. Applicants submit that the specification is also enabling for methods for inhibiting proliferation or migration of smooth muscle cells *in vitro* as well as *in vivo* (see, for example, page 55, line 14 to page 62, line 11).

The Prima Facie Case Has Not Been Made

The Federal Circuit has cited the United States Court of Customs and Patent Appeals' statement that "[A] specification disclosure which contains a teaching in the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented

must be taken as in compliance with the enabling requirement of the first paragraph of S. 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)" cited in In re Brana, 51 F.3d 1560, 1566.

Applicants respectfully submit that an Examiner must provide a reasonable explanation as to why the scope of the protection provided by a claims is not adequately enabled by the disclosure (In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); M.P.E.P. §2164.04):

"it is incumbent upon the Patent Office ... to explain *why* it doubts the truth or accuracy of any statement in the supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. " In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370.

Similarly, the M.P.E.P. at §2164.04 notes that "[a]ccording to In re Bowen, 492 F.2d 859, 862-3, 181 USPQ 48, 51 (CCPA 1971), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement." Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Although the Examiner has acknowledged that the specification is enabling for an *in vitro* method of partially inhibiting proliferation or migration of vascular smooth muscle cells in cell culture, the Examiner suggests that the "specification does not teach how to extrapolate data obtained from an *in vitro* assay studies to the development of effective *in vivo* mammalian therapeutic treatment" (Office action mailed September 9, 2004, page 3, lines 33-35) and that "since no animals were used as model system to inhibite (sic) proliferation or migration of vascular smooth muscle cells *in vivo*, it is not clear that reliance on the *in vitro* data that culturing human aortic smooth muscle cells in the presence of effective amount of antibody to native ErbB4 receptor will reduce cell proliferation" (Office action mailed September 9, 2004, page 3, lines 20-24).

A mere assertion by the Examiner that "it is not clear that reliance on the *in vitro* data that culturing human aortic smooth muscle cells in the presence of effective

amount of antibody to native ErbB4 receptor will reduce cell proliferation" does not meet the Patent and Trademark Office's burden to adequately explain *why* there might be doubt as to the *in vivo* efficacy of the present methods, nor does such an assertion provide acceptable evidence or reasoning which is inconsistent with the contested statements.

Applicants note that the Court of Customs and Patent Appeals stated (when discussing the utility of an invention) that "No authority has been cited and we have been able to find none which requires that in order to secure a patent, utility of a pharmacologically active substance must be proved by *in vivo* testing." In re Isaacs and Lindenmann, 146 USPQ 193, 195 (1965).

In particular, applicants note that *in vitro* data may support claims to *in vivo* methods (see, e.g., In re Brana, 51 F.3d 1560, 1561, 34 USPQ2d 1436,1441 (Fed. Cir. 1995, as cited at M.P.E.P. §2164.01(a)). The legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in Cross v. Iizuka, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

"We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. §2107.03 (III) states that:

"If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Thus, Applicants respectfully submit that for the Examiner to merely suggest that "it is not clear that reliance on the *in vitro* data that culturing human aortic smooth muscle cells in the presence of effective amount of antibody to native ErbB4 receptor will reduce cell proliferation" without a reasonable explanation as to why the Examiner believes that the scope of the claims is not adequately enabled by the disclosure is not a sufficient basis to reject the claims as allegedly not enabled.

The Specification Provides Support for the Claimed Invention

Applicants note that the specification teaches how to make and use the invention. The specification presents data showing reduced proliferation (Example, 2, pages 67-68) and showing reduced migration (Example 3, pages 68-69) as a result of treatment with novel antibody antagonists (e.g., novel immunoadhesins) useful for the claimed methods. These data indicate that the novel immunoadhesins of the Examples are able to inhibit proliferation and migration of smooth muscle cells as claimed. The specification thus provides support for the scope of the protection provided by a claims, which applicants submit are adequately enabled by the disclosure. For example, the specification teaches and provides examples regarding the claimed therapeutic compositions and novel methods and disease conditions susceptible of treatment by them (see, e.g., pages 55-62), including explicit dosage ranges (page 62); methods for identifying molecules that affect proliferation or migration of smooth muscle cells (see, e.g., pages 62-65); methods for making the novel immunoadhesins disclosed in the specification (see, e.g., pages 65-67); effects of the novel immunoadhesins on human aortic smooth muscle proliferation (see, e.g., 67- 68); and effects of the novel immunoadhesins on human aortic smooth muscle migration (see, e.g., 68-69).

Applicants note that the specification teaches amounts and methods of the disclosed pharmacological agents that may be used to practice the invention (see, e.g., the *in vitro* examples, such as at page 67, line 25; page 68, line 16; and Table 3, page 71-72, and page 72, line 15). The Federal Circuit, discussing utility, stated that "there is reasonable correlation between the disclosed *in vitro* utility and *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of

pharmacological activity is reasonable based upon the probative evidence." Cross v. Iizuka, 752 F.2d 1040, 1050 (Fed. Cir. 1985). As noted above, the specification provides disclosure of pharmacological activity of the novel compositions in *in vitro* models of diseases based on cultures of the human cells affected in the target disease conditions.

There is a Nexus Between the *in vitro* Models and *in vivo* Efficacy

The *in vitro* assays disclosed in the specification utilize human smooth muscle cells in culture. Hyperplasia and hypertrophy of human smooth muscle cells *in vivo* are implicated, for example, in chronic severe asthma (Krymskaya et al., *Am. J. Physiol.* 276:L246-L255 (1999)). *In vitro* assays using human airway smooth muscle cells (Krymskaya et al.), vascular smooth muscle cells (Wakino et al., "Retinoids Inhibit Proliferation of Human Coronary Smooth Muscle Cells by Modulating Cell Cycle Regulators," *Arterioscler Thromb Vasc Biol* 21:746-751 (2001)) and other cells (e.g., Lauder et al., "Quantification of the repair process involved in the repair of a cell monolayer using an *in vitro* model of mechanical injury," *Angiogenesis* 2(1):67-80 (1998)) were well known at the time the application was filed, and were accepted as relevant to clinical questions. Applicants note, for example, that Poon et al. ("Rapamycin Inhibits Smooth Muscle Cell Migration," *J. Clin. Invest.* 98:2277-2283 (1996)), based on their *in vitro* results, followed up with further *in vitro* and also *in vivo* experiments, which results were published in a clinical journal. Thus, such *in vitro* assay results as disclosed in the present application were recognized in the art as indicative of similar applicability *in vivo*.

As was discussed above, Applicants submit that merely suggesting that "it is not clear that reliance on the *in vitro* data ... will reduce cell proliferation" does not provide a reasonable explanation as to why the scope of protection provided by the claims is not adequately enabled by the disclosure, and so fails to meet the burden required by statute and case law to rebut the enablement of the disclosure (In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); MPEP 2164.04). Moreover, in the present

case, even if the Examiner had met the burden (which he has not), Applicants have overcome the rejection by providing *in vitro* data for the claimed methods of inhibiting proliferation or migration of smooth muscle cells, using art recognized assays recognized as correlating with *in vivo* results. As discussed above, one of ordinary skill in the art reading the written description contained in the specification, and based on the art-recognized assays and art-recognized correlation between *in vitro* data and *in vivo* activity, would have recognized that Applicants have enabled the claimed invention.

Accordingly, Applicants respectfully submit that the rejections of Claims 1, 10-11, 23-27 and 85-89 under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to be enabling is overcome. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The Rejection of Claim 26 Under 35 U.S.C. §112, Second Paragraph

Claim 26 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the Examiner alleging that the claim is indefinite and ambiguous in the recitation of the phrase "antibody binds essentially the same epitope as an antibody produced by ...," the phrase "essentially the same epitope" allegedly being unclear. Applicants respectfully traverse this rejection, for at least the reason that an antibody that binds "essentially the same epitope" is clearly defined in the specification (e.g., page 21, lines 26-30, to page 22, lines 1-2), and would be understood by one of ordinary skill in the art. However, solely to expedite prosecution of the claims to issuance, applicants have amended Claim 26 to include "wherein said antibody competes for binding" in the claim. Thus, as amended, Claim 26 now recites the phrase "wherein said antibody competes for binding to the epitope bound by the antibody produced by a hybridoma ..." and not the phrase the phrase "essentially the same epitope" that had been objected to by the Examiner.

Claim 26 is directed to methods for inhibiting proliferation or migration of vascular smooth muscle cells by treating the target cells with an antibody that "competes for

binding to the epitope bound by the antibody produced by ..." one of the named, novel hybridoma cell lines. Support is found in the definition of the phrase "essentially the same epitope" at page 21, line 26 to page 22, line 2. Accordingly, Applicants respectfully submit that the rejection of Claim 26 under 35 U.S.C. §112, second paragraph, has been overcome.

The Rejection of Claims 1, 10-11, 23-27 and 85-89 Under 35 U.S.C. §112, Second Paragraph

Claims 1, 10-11, 23-27 and 85-89 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the Examiner stating that this rejection was "necessitated by the amendment filed August 9, 2004." Independent Claims 1, 26, and 27 were alleged to be indefinite and ambiguous in the recitation of "treating said vascular smooth muscle with ... antibody antagonist ..." The Examiner alleged that it was unclear whether an antibody or whether an antagonist of said antibody was to be used. Applicants respectfully traverse these rejections.

The claims have been amended to recite an "antagonist antibody." Applicants note that ErbB4 antagonists are defined in the specification, for example, at page 12, lines 21 through page 13, line 6. The explicit definition of ErbB4 antagonists includes antibody antagonists, *i.e.*, antagonists that comprise antibodies, such as: "neutralizing antibodies against native sequence ErbB4 receptors, neutralizing antibodies to ligands of native sequence ErbB4 receptors (e.g., anti-HB-EGF antibodies), ErbB4-Ig immunoadhesins (including chimeric immunoadhesins)" (see, e.g., page 13, lines 3-6). Antagonist antibodies are mentioned, e.g., at page 45, lines 16-18; page 47, lines 2-3 and 16-18; page 48, lines 19012 and 16-18; page 50, lines 11-13; and page 51, lines 23-29. Neutralizing antibodies are defined in the specification, for example, at page 20, lines 1-23. Inhibition of ErbB4 receptors is discussed in the specification, for example, at page 22, lines 3-11. Stenosis and other diseases involving smooth muscle proliferation are disclosed as being susceptible of treatment by "antagonists of native ErbB4 receptors" such as immunoadhesins and chimeric heteromultimer adhesins, as

discussed at page 24, lines 2-4, page 57, lines 27-28, and elsewhere in the specification.

The specification explicitly defining the subject term, and including further explanation and discussion regarding the term "antagonist antibody," Applicants respectfully submit that the term "antagonist antibody" is clear to one of ordinary skill in the art. Accordingly, Applicants believe the rejection of Claims 1, 26, and 27 under 35 U.S.C. §112, second paragraph to be overcome, and that the rejection of Claims 1, 10-11, 23-27 and 85-80 under 35 U.S.C. §112, second paragraph to be overcome.

The Rejections of Claims 1, 10, 11, and 23-26 Under 35 U.S.C. §103(a)

Claims 1, 10, 11, 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,811,098 (Plowman) in view of Krymskaya (1999) or WO 99/02681 (Godowski), for the reasons set forth in the previous Office Action mailed March 9, 2004.

In order to establish a *prima facie* case of obviousness, there must be: 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the Applicants' disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The U.S. Court of Appeals for the Federal Circuit has held that

[t]he PTO has the burden under section 103 to establish a *prima facie* case of obviousness . . . It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The case law is also clear that the motivation to support a combination of references in a Section 103 rejection must withstand scrutiny.

In In re Rouffet, 149 F.3d 1350; 47 USPQ2d 1453 (Fed. Cir. 1998), the CAFC reaffirmed that a suggestion to combine known elements present in various pieces of prior art is critical for establishing a *prima facie* case of obviousness. The CAFC observed that:

“[V]irtually all [inventions] are combinations of old elements.” Environmental Designs, Ltd. V. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2s 1573, 1579-80, 219 U.S.P.Q. 8, 12 (Fed. Cir. 1983) (“Most, if not all, inventions are combinations and mostly of old elements.”). Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such approach would be “an illogical and inappropriate process by which to determine patentability.” Sensonics, Inc. v. Aerasonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996).

In re Rouffet, 149 F.3d at 1357 47 U.S.P.Q.2d at 1457

The requirement that an examiner must show a suggestion to combine references cited in support of an obviousness rejection is a critical safeguard against hindsight reconstruction of an invention. The motivation to modify a reference can come from: (1) the nature of the problem to be solved, (2) the teachings of the prior art itself, or (3) the knowledge of persons of ordinary skill in the art. In re Rouffet, 149 F.3d at 1358; 47 U.S.P.Q.2d at 1458.

Applicants submit that the Examiner has failed to establish a *prima facie* case that the claimed invention is obvious over the cited references.

For the sake of brevity, Applicants' remarks and arguments presented in prior papers regarding the rejections of the claimed inventions as allegedly being obvious over Plowman (U.S. Patent No. 5,811,098) in view of Krymskaya or Godowski (WO 99/02681) are hereby incorporated by reference. Applicants note, however, that Applicants' prior remarks and arguments include noting (as was also stated by the

Examiner) that Plowman is directed to cancer cells, and does not provide nor suggest a method for controlling excessive proliferation or migration of smooth muscle cells; that Godowski nowhere suggests that antagonists to ErbB4 receptors might be useful to control smooth muscle proliferation; and that Krymskaya teaches that ErbB4 receptors are inactive on airway smooth muscle cells.

Applicants acknowledge the Examiner's statement that "unobviousness cannot be established by attacking the references individually when the rejection is based upon the combination of the references" (page 5, lines 8-10, citing In re Keller and In re Young). As in previous responses, in the present response applicants address the failure of the *combined* references to make obvious the claimed invention. As noted in previous responses, Applicants submit that there is no motivation in the references or in the art to combine the references, nor do the cited references provide a reasonable expectation of success for such a combination were it to be made. In addition, applicants submit that an assertion that it may be "obvious to try" a course of action or method is not a proper nor sufficient basis for an obviousness rejection. Each of these issues is addressed in the following discussion.

There is no motivation to combine the cited references

Applicants submit that there is no motivation in the references or in the art to combine the references. For example, Plowman is directed to cancer cells, not smooth muscle cells; Godowski, although mentioning that smooth muscle cells are among the cell types that may have ErbB4 receptors, does not discuss proliferation or migration of smooth muscle cells; and Krymskaya teaches that "... in quiescent HASM [human airway smooth muscle] cells, ErbB-3 and ErbB4 are functionally inactive" (page L252, column 2, lines 7-9) and "ErbB-3 and ErbB4 in EGF-stimulated cells did not appear to be activated" (page L248, column 2, lines 37-39).

Krymskaya

The Examiner suggests that Krymskaya, teaching the presence of ErbB4 receptors, "teach that this receptor play a pivotal role in the regulation of proliferation of smooth muscle cells," directing the applicant's attention to the abstract and to page

L254. Applicants respectfully note that careful inspection of the Abstract and of page L254, and of the remainder of the Krymskaya reference, does not reveal any suggestion that the ErbB4 receptor plays a role, much less a pivotal role, in the regulation of proliferation of smooth muscle cells.

The Krymskaya abstract, discussing the epidermal growth factor receptor (EGFR) family, says: "This receptor family plays a pivotal role in regulating cell proliferation, differentiation, and transformation." Applicants note that it does not say that ErbB4 receptor plays such a role; in fact, it explicitly says just the opposite: "ErbB3 and ErbB4 are present in HASM cells; *however, EGF has no effect on their activation.*" (emphasis added; HASM indicates human airway smooth muscle cells). Thus, the Krymskaya abstract explicitly teaches away from the position that the Examiner suggests that it supports.

Page L254 of Krymskaya, also cited by the Examiner, also teaches away from the Examiner's position, and so fails to support it. Page L254, column 1, lines 17-22 state: "EGFR and ErbB-2 were activated by betacellulin *but not ErbB-3 or ErbB4*. Although all EGFR family members are expressed in quiescent HASM cells, our data suggest that *ligand-induced signaling involves only EGFR and ErbB-2 activation.*" (emphasis added).

Thus, Applicants reiterate that Krymskaya does not suggest any role for ErbB4 in proliferation of HASM, nor does it suggest that antibody antagonists to native ErbB4 receptors of SEQ ID NO: 2 might be useful in inhibiting proliferation or migration of smooth muscle cells.

Since Krymskaya teaches that ErbB4 receptors are *functionally inactive* in airway smooth muscle cells, one of ordinary skill in the art would not be motivated to treat such cells with a ligand that interacted with ErbB4 receptors, and would reasonably expect that no effect would result from such treatment. Thus, there is no teaching in Krymskaya that would suggest or motivate one of ordinary skill in the art to combine its teachings with any other reference to provide an invention directed towards interacting

with ErbB4 receptors of SEQ ID NO: 2 to inhibit proliferation or migration of smooth muscle cells.

Godowski

The Examiner also suggests that "WO 99/02681 teaches the presence of ErbB4 receptor on smooth muscle cells and that blocking signal transduction pathway mediated through this receptor can effect mitotic activity of cells expressing said receptors (see entire document, page 8, lines 35-40 and page 17, lines 27-35 in particular). Inspection of the entire document, and of the cited pages in particular, shows that Godowski (WO 99/02681) does include "smooth muscle cells" among the many cell types named as comprising the ErbB4 receptor (page 8, lines 38-39). "Neutralizing antibodies" are defined in that reference as "an antibody molecule as herein defined which is able to block or significantly reduce an effector function of NRG3." Such a neutralizing antibody "may also block the mitogenic activity of NRG3 in the cell proliferation assay disclosed herein" (page 17, lines 30-31).

Although Godowski discusses a ligand (NRG3) that interacts with ErbB4 receptors, and mentions that ErbB4 receptor-containing cells include smooth muscle cells (page 8, lines 38-39), Godowski nowhere discusses interaction with ErbB4 receptors of SEQ ID NO: 2 on smooth muscle cells in order to affect smooth muscle cell proliferation or migration. Accordingly, Godowski also provides no motivation to combine its teachings with any other reference to provide an invention directed towards ErbB4 receptors of SEQ ID NO: 2 to inhibit proliferation or migration of smooth muscle cells.

Plowman

The Examiner also cites column 22, lines 44-66 of Plowman, for example, as suggesting that antibodies to HER4 may be used to inhibit undesirable cell function and behavior, "including proliferation and migration" (quoting the Examiner, page 6, lines 4 of the Office action dated September 9, 2004). However, although column 22, lines 44-66 of Plowman discusses "inhibiting undesirable biological responses" (column 22, line 45), such undesirable biological responses do not include proliferation

and migration of smooth muscle cells. The only mention of cell proliferation is with regard to breast cancer cells in culture (column 3, line 51); there is no mention of cell migration (the only instance of the word "migration" is with respect to the migration of a protein on a gel; column 51, line 40).

As discussed previously, Plowman does not mention smooth muscle. Thus, although Plowman discusses antibodies to native HER4 receptor, that reference's discussion of *cancer cells* in no way suggests applications directed to inhibition of proliferation or migration of smooth muscle cells. The Examiner acknowledges that Plowman does not teach a method of controlling excessive proliferation or migration of smooth muscle cells (page 6, lines 9-10 of the Office action mailed September 9, 2004).

Thus, for these reasons at least, there is no motivation to combine the cited references in an attempt to provide the claimed methods which are directed toward inhibiting proliferation or migration of smooth muscle cells utilizing an antibody antagonist of a native ErbB4 receptor of SEQ ID NO: 2.

The combination of the cited references fails to provide the claimed invention

Although ErbB4 receptors are mentioned in the cited references, as discussed above, the cited references do not provide any suggestion to be combined to provide the claimed invention. Applicants note that the Federal Circuit has stated that "[O]bvious to try is not the standard" (Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000)) and that "[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 USC 103." (Gillette Co. v. S. C. Johnson & Son, Inc., 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997)). Thus, such mere mention of one of the elements of the claimed invention, without more, does not make the claimed invention obvious.

In addition, even if combined, the references fail to make obvious the claimed invention.

The cited references mention *i*) that ErbB4 receptors may be present on smooth muscle cells (Godowski, Krymskaya), *ii*) that there may be antibodies to such receptors

(Plowman, Godowski), and *iii*) that such receptors are inactive in airway smooth muscle (Krymskaya). Combining these suggestions, we find that inactive ErbB4 receptors may be present on smooth muscle cells, and that antibodies to such inactive ErbB4 receptors may be made.

However, the combined references fail to provide any suggestion that ErbB4 receptors might play a role in smooth muscle proliferation or migration, or that such a (non-existent) role could be antagonized, or that antibodies to ErbB4 receptors may have an effect on smooth muscle proliferation or migration.

The invention of Claim 1 provides "a method for inhibiting proliferation or migration of smooth muscle cells comprising treating said smooth muscle cells with an effective amount of an antagonist antibody of a native ErbB4 receptor of SEQ ID NO.: 2" and so requires, among many elements, (a) an antagonist antibody of a native ErbB4 receptor of SEQ ID NO.: 2, (b) inhibition of proliferation or migration of smooth muscle cells by treatment with an antagonist antibody of a native ErbB4 receptor, and (c) treatment with an effective amount of an antagonist antibody of a native ErbB4 receptor of SEQ ID NO.: 2. As discussed above, the combination of the cited references fails to provide either (a), (b), or (c) as applied to smooth muscle cells. The combined references do not provide any suggestion that an antibody antagonist of a native ErbB4 receptor could be used to treat a smooth muscle cell effective to inhibit proliferation or migration of a smooth muscle cell. Moreover, the teaching by Krymskaya that such ErbB4 receptors are inactive on human airway smooth muscle cells teaching away from the present invention, the combined references do not suggest that there could be *an effective amount* of such an antibody antagonist. Thus, the combination of the cited references fails to provide at least several of the required elements of the claimed invention of Claim 1. Claims 10, 11, and 23-26 require all the elements of Claim 1, and provide additional elements as well. Thus, the combination of the cited references failing to make Claim 1 obvious, the combined references also fails to make Claims 10, 11, and 23-26 obvious.

Applicants note that the antibodies recited in the method of Claim 26 bind the epitope that is bound by the antibody produced by one of the named, novel hybridoma

cells. Such antibodies, hybridomas, and epitopes for which the novel antibodies from the novel hybridomas compete for binding are nowhere disclosed, and nowhere suggested, by any combination of the cited references. Accordingly, Applicants submit that, for this reason at least, in addition to the other reasons previously discussed, Claim 26 is not made obvious by any combination of the cited references.

Thus, even taken in combination, the cited references fail to make obvious the claimed invention. No combination of the cited references suggest that an antibody antagonist to a native ErbB4 receptor might act on a smooth muscle so as to inhibit smooth muscle proliferation or migration. Thus, even taken together, the references fail to provide or suggest at least this element of the claims.

The combination of the cited references does not provide a reasonable expectation of success for claimed invention

As was also discussed previously, for at least the reasons discussed above, one of ordinary skill in the art would have no reasonable expectation of success even if the references were to be combined. None of the references suggest that ErbB4 receptors are involved with proliferation or migration of smooth muscle cells; in fact, Krymskaya states that ErbB4 receptors are not active in HASM cells. Thus, in view of the teachings of the cited references, one of ordinary skill in the art would not expect an antibody antagonist of a native ErbB4 receptor of SEQ ID NO: 2 to inhibit proliferation or migration of smooth muscle cells. Accordingly, the cited references fail to provide a reasonable expectation of success for the claimed invention.

Accordingly, the cited references failing to provide all the elements of the claimed invention, failing to suggest or provide motivation to provide such elements or to be combined in an attempt to do so, and failing to provide a reasonable expectation of success for such a combination, Applicants submit that the Examiner has failed to provide a *prima facie* case of obviousness.

Moreover, even if the Examiner had provided a *prima facie* case of obviousness under 35 U.S.C. §103, such a case is rebutted by the references cited by the Examiner. As discussed above, Krymskaya explicitly teaches away from the claimed invention,

stating that ErbB4 receptors in human airway smooth muscle are inactive (Krymskaya, page L248, column 2, lines 37-39 and page L252, column 2, lines 7-9).

Applicants note that the Federal Circuit has stated that "A *prima facie* case of obviousness can be rebutted if the applicant . . . can show 'that the art in any material respect taught away' from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997) (quoting *In re Malagri*, 499 F.2d 1297, 1303, 182 USPQ 549, 533 (CCPA 1974)). Teaching away has been defined by the Federal Circuit: "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999). It is clear that Krymskaya, teaching that ErbB4 receptors on HASM are inactive, teaches away from the claimed invention in a material way. It is also clear that one of ordinary skill, reading Krymskaya, would be taught that interactions with ErbB4 receptors would be ineffective for inhibiting proliferation or migration of smooth muscle cells, and thus would be led away from the path taken by the present Applicants.

Accordingly, the Examiner having failed to provide a *prima facie* case of obviousness, and the cited references rebutting such a *prima facie* case if it had been provided, Applicants respectfully submit that the rejections of Claims 1, 10, 11, and 23-26 under 35 U.S.C. §103(a) are overcome.

CONCLUSION

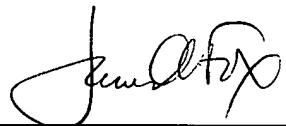
Applicants believe all rejections to be overcome by the amendments and arguments above, and request reconsideration and allowance of all pending claims. All claims being believed to be in *prima facie* condition for allowance, an early action to that effect is respectfully solicited.

If any rejections or objections remain, Applicants request that an interview with the Examiner, either in person or via telephone, before the issuance of the next Action in this case to allow discussion of such issues as may remain.

Please charge the fees for extension of time, and any additional fees that may be required, or credit overpayment to Deposit Account No. 08-1641, referencing Attorney's Docket No. 39766-0072 A2.

Respectfully submitted,

Date: December 22, 2004

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